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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,504	11/19/2001	Michael E. Himmel	NREL 99-38	3921

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/25/2003

(0)

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,504	HIMMEL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21, 26- 28* is/are pending in the application.

4a) Of the above claim(s) *1,2,9-21 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-21, 26 through 28 are still at issue and are present for examination. Claims 3-4 and 5-8 are now under consideration. Claims 1-2, 9-21, 26-28 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group II, Claims 3-8 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that applicants have now filed a linking claim and encompassing claims of groups I, II, IV and V and that the linking claim must be examined with he elected claim. Examiner respectfully disagrees with such a conclusion by the applicant. Linking claims that act to prevent restriction between inventions are A) genus claims linking species, B)a claim to the necessary process of making a product, linking process and product claims, C)a claim to "means", for practicing a process linking proper apparatus and process claims; and D)a claim to the product linking a process of making and a use, MPEP 809.03. However, claims 26 and 27 do not form proper "linking claims" and in fact could be grouped into a separate group by itself. This is because first of all claim 1 is not specifically not drawn to a method of making a product. It is drawn to a method of improving a product. Therefore, while the claims (i.e., claims 26 and 27) claiming the method of improving the specific activity by the combination of replacing hydrophobic surface binding amino acids and replacing an active site associated glycosyl-stabilizing amino acid may be allowable and enabled, the individual methods by themselves, i.e., replacing hydrophobic surface binding amino acids or replacing an active site associated glycosyl-stabilizing amino acid may not be enabled and

therefore not allowable. Under such circumstances even though the linking claim is allowable, the linked claims cannot be automatically allowed.

Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-2, 9-21, 26-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants fail to provide appropriate SEQ ID NOs to sequences recited in the specification on pages 28-30. See particularly 37 CFR 1.821(d).

Claim Objections

Claims 5 through 8 are objected to because of the following informalities: Claims 5-8 continues to depend from non-elected claim 1. Appropriate correction is required.

Claim 7 is objected to because of the following informalities: Claim 7 recites amino acid positions in an amino acid sequence. It would be impossible for the Examiner to search these claims without a SEQ ID NO for the mutant glycosyl hydrolase enzyme. Examiner urges the applicants to provide appropriate SEQ ID NO while referring to individual amino acid positions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 and claims 4-8 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the phrase "increasing the specific activity" rendering the claim indefinite. The metes and bounds of the term "increasing" is not clear to the Examiner. It is also not clear to the Examiner as to how much activity is considered as increased activity and with reference to the activity of which enzyme. Without a specific numerical value quantifying the increased specific activity, the above phrase renders the claim indefinite. Correction is required.

Claim 3 and claims 4-8 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the phrase "not strongly retarding" rendering the claim indefinite. The metes and bounds of the term "strongly" is not

clear to the Examiner. It is also not clear to the Examiner as to how much retardation is considered as "strong retardation" by the applicant. Without a numerical value quantifying the retardation, the above phrase renders the claim indefinite. Correction is required.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the phrase "tyrosine 3" rendering the claim indefinite. It is not clear to the Examiner as to what applicants mean by "tyrosine 3". Correction is required.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase "wherein replacing comprises site-directed mutagenesis" rendering the claim indefinite. It is not clear to the Examiner as to what applicants mean by the above phrase. It appears that applicants intended to recite that the method used for replacing the amino acids was by site-directed mutagenesis. If this is so appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the specific activity of EI endoglucanase on pretreated biomass, isolated from *Acidothermus cellulolyticus* comprising the replacement of

the specific active site associated glycosyl stabilizing amino acid, tyrosine at position 245 in the respective amino acid sequence depicted under Example 7 in the specification, does not reasonably provide enablement for a method of increasing the specific activity of any glycosylhydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 3-5 and 8 are so broad as to encompass a method of increasing the specific activity of any glycosylhydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the application of a single method for an extremely large number of glycosylhydrolases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's

sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the single EI endoglucanase isolated from *A.cellulolyticus* and comprising the amino acid sequence as depicted in Example 7 of the specification. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to a method of enhancing the specific activity of a single EI endoglucanase against a single substrate, i.e., pretreated biomass, but provides no guidance with regard to using the same method for any glycosylhydrolase isolated from any source and having any structure. In view of the great breadth of the claim, amount of experimentation required to use the above method on any glycosylhydrolase which includes a large number of different hydrolytic enzymes acting on a wide range of substrates, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the method encompassed by these claims.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses a method of increasing the specific activity of any glycosylhydrolase enzyme isolated from any or all sources acting on any or all type of substrates, comprising the replacement of any active site associated glycosyl stabilizing amino acid because the specification does not establish that: (A)the method works in all or any glycosylhydrolases which includes a large number of different enzymes; (B) the specific activity of the glycosylhydrolases is enhanced irrespective of the type of substrate; (C) a rational and predictable scheme for identifying and modifying any active site residue in any glycosylhydrolase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any glycosylhydrolase and all or any type of substrates. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a method that applies to all types of glycosylhydrolases and all types of substrates is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 3-5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

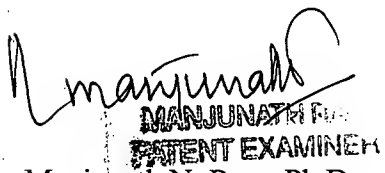
Claims 3-5 and 8 are directed to a method of enhancing the specific activity of any glycosylhydrolase. Claims 3-5 and 8 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides that have not been disclosed in the specification. No description has been provided of the polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single specific polypeptide having EI-endoglucanase activity and isolated from A.cellulolyticus (in Example 7) has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of the polypeptide sequences within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804.. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao. Ph.D.
July 16, 2003